Rovedar

Research in Biotechnology and Environmental Science. 2022; 1(2): 36-42.
DOI: 10.58803/rbes.v1i2.7
http://rbes.rovedar.com/

Reveiw Article

Bacterial Resistance of *Acinetobacter baumannii:* A Global Concern

Ali Qasemi[1], Zeynab Bayat[2], Nazanin Akbari[3], and Daryoush Babazadeh[4,*]

[1] Department of Biology, Faculty of Sciences, University of Sistan and Baluchestan, Iran
[2] Department of Biology, Faculty of Sciences, Shahid Bahonar University of Kerman, Kerman, Iran
[3] Department of Biology, Faculty of Sciences, Shahid Beheshti University, Tehran, Iran
[4] Department of Clinical Sciences, Faculty of Veterinary Medicine, Shiraz University, Shiraz, Iran

*** *Corresponding author:*** Daryoush Babazadeh, Department of Clinical Sciences, Faculty of Veterinary Medicine, Shiraz University, Shiraz, Iran.
Email: daryoush.babazadeh@shirazu.ac.ir; Daryoushbabazadeh@gmail.com

ARTICLE INFO

Article History:
Received: 25/08/2022
Accepted: 10/10/2022

Keywords:
Acinetobacter baumannii
Antibiotic
Multidrug resistance

ABSTRACT

Acinetobacter baumannii (*A. baumannii*), one of the five most important bacteria with global threat to human health due to constantly increasing resistance (ESKAPE organisms), identified as a enormous threat in healthcare facilities, can create antibiotic resistance. The implementation of early detection and identification of multidrug-resistant *A. baumannii* is serious to control its spread. The this study presents the human infection of *A. baumannii*, pathological findings, virulence factors of *A. baumannii*, antibiotic resistance mechanisms, and the therapeutic options available for treating *A. baumannii* infections. The ability of *A. baumannii* to develop antibiotic resistance mechanisms allows the organism to prosper in hospital settings, facilitating the global spread of multidrug-resistant strains. To dominate this problem, knowledge of the pathogenesis and antibiotic resistance mechanisms of *A. baumannii* is important. As reported, *A. baumannii* resistance to aminoglycosides, fluoroquinolones, and carbapenems increased, and resistance to lipopeptides, such as polymyxin B and colistin, are lower compared to that of other antimicrobial drugs. Therefore, novel prevention and treatment strategies against *A. baumannii* infections are warranted.

1. Introduction

Antimicrobial or antibiotic resistance (AMR) is an important and triggering phenomenon with increasing costs for healthcare systems worldwide. In recent years, AMR has been related to significant morbidity, mortality, and increased costs resulting from prolonged hospitalization and treatment. Data from multicenter studies in the previous decades have demonstrated an increase in both community-acquired and nosocomial AMR as well as a rise in the number of older patients with primary or secondary immunodeficiencies[1,2].

The World Health Organization (WHO) has long recognized the need for an improved and coordinated global effort to contain AMR[3,4]. The first WHO Global report on AMR surveillance was conducted on national and international surveillance networks for the first time, indicating the extent of AMR surveillance in different parts of the world and the presence of large gaps in the existing surveillance[4].

Acinetobacter baumannii (*A. baumannii*) belongs to the Moraxellaceae family and is a Gram-negative bacterium that predominantly causes nosocomial infections. *Acinetobacter* taxonomy involves phenotypic traits and chemotaxonomic methods[5]. *Acinetobacter baumannii* is part of the *A. baumannii* - *A. calcoaceticus* complex (Acb), initially including four species, namely *A. calcoaceticus*, *A. baumannii*, *A. nosocomialis*, and *A. pittii*[4]. Subsequently, several other species, such as *A. seifertii*, have been proposed for inclusion in this complex[5], *A. lactucae*[6], and *Acinetobacter* species between 1 and 3[6].

Acinetobacter infections include meningitis, urinary tract infections, hospital-acquired (HAP) and ventilator-associated pneumonia (VAP), bacteremia, and gastrointestinal and skin/wound infections[7]. Gupta et al. observed that the infection was common in patients aged group >50 years followed by those younger than 10 years old[8], indicating a wide range of infections at different ages. Due to clusters of closely related species, distinguishing Acinetobacter species is difficult. Among *Acinetobacter* species, Acinetobacter baumannii is the most important member associated with

► *Cite this paper as*: Qasemi A, Bayat Z, Akbari N, Babazadeh D. Bacterial Resistance of *Acinetobacter baumannii:* A Global Concern. Research in Biotechnology and Environmental Science. 2022; 1(2): 36-42. DOI: 10.58803/RBES.2022.1.2.01

hospital-acquired infections worldwide[9].

Acinetobacter baumannii is one of the ESKAPE organisms (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *A. baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.) that pose a global threat to human health and a therapeutic challenge due to constantly increasing resistance[10]. Resistance of *A. baumannii* isolates to broad-spectrum antibiotics, such as amikacin, expanded-spectrum cephalosporins, carbapenems, and tigecycline is on the rise, so physicians are increasingly left with very few effective therapeutic options[11]. Carbapenem-resistant A. *baumannii* (CRAB) was ranked in 2018 by WHO as the number one priority for antibiotic research and development. Carbapenem was chosen as a marker because carbapenem resistance is usually associated with a broad range of co-resistance to other antibiotic classes[12]. Imipenem-resistant *A. baumannii* constituted more than 50% of a worldwide collection of clinical trials between 2005 and 2009[13].

The overall prevalence of multidrug-resistant strains in patients with *A. baumannii* HAP and VAP is estimated to be 79.9%, ranging from 56.5% in Argentina and 61.8% in Taiwan to 100% in Central America, Pakistan, Lebanon, Qatar, and Croatia, while its overall mortality can be as high as 56.2%[14]. The patterns of carbapenem resistance differ throughout Europe and also within the countries of the Arab League. Increased incidence of carbapenem-resistant *A. baumannii* isolates has been observed in Northern and Eastern Europe as well as in the Levant countries of the Arab League (Iraq, Jordan, Lebanon, Palestinian territories, and Syria)[15]. This aerobic Gram-negative coccobacillus had been regarded as a low-grade pathogen, but is a successful pathogen responsible for opportunistic infections of the skin, bloodstream, urinary tract, and other soft tissues[16]. Since many *A. baumannii* infections have suddenly been reported among veterans and soldiers who served in Iraq and Afghanistan[17], *A. baumannii* is referred to as Iraqibacter. The frequency of community-acquired *A. baumannii* infections has increased gradually[18]. Many reports have shown that isolates of *A. baumannii* rapidly develop resistance to antimicrobials and multidrug-resistant strains[19].

A systematic review concluded that the acquisition and spread of *A. baumannii* appeared to be related to a large number of variables, the most important of which were deficiencies in the implementation of infection control guidelines and the use of broad-spectrum antibiotics[20].

Moradi in Iran found that the antimicrobial resistance of *A. baumannii* has increased, which may affect the antimicrobial resistance of this organism worldwide[21].

This review summarizes the role of *A. baumannii* in human infectious pathology, virulence factors of *A. baumannii*, antibiotic resistance mechanisms, and the therapeutic options available for treating *A. baumannii* infections.

2. Risk factors

Age, respiratory and cardiovascular system diseases, diabetes mellitus, high APACHE 2 score, immune-suppression, antibiotic use, hospitalization before infection, especially in intensive care units (ICUS), central venous and nasogastric catheter, mechanic ventilation are listed as risk factors of *A. baumannii* infections. Transfusion, hemodialysis, and trauma are not known as risk factors for this infection[22].

Comorbidities refer to hypertension, coronary heart disease, diabetes, cancer, chronic renal insufficiency, and cerebral infarction; ICU days refer to patients with ICU admission until they test positive for the first time. The combination of antimicrobial agents is the use of two or more than two kinds of antibacterial drugs. Invasive operation refers to a tracheotomy, nasal feeding, indwelling catheter, arteriovenous catheter, abdominal puncture, and ventilator[23].

Chiang and Silvia Munoz et al. also found that the tumor underlying disease is a risk factor causing the death of patients with *A. baumannii* bloodstream infection[24, 25].

In previous studies, risk factors of *A. baumannii* bloodstream infection included serious underlying illnesses, exposure to antibacterial drugs, colonization of bacteria, history of surgery, central venous catheter and indwelling catheter, parenteral alimentation, mechanical ventilation as well as time in ICU[26].

3. Virulence *factors of Acinetobacter baumannii*

Several effective factors can play a role in the disease process caused by *A. baumannii*[27]. Table 1 demonstrates the important virulence factors and their role in *A. baumannii* pathogenesis.

Pieces of evidence elucidated these virulence factors, including adherence and invasion in host cells and host cell death, outer membrane protein A (OmpA), phospholipids, extracellular polysaccharides capsule, siderophore-mediated iron-acquisition system, phospholipases, and biofilm formation have an important role in bacterial pathogenicity[28].

These virulence factors, along with MDR trait, make this pathogen create havoc, at least in hospitals, and act as the emerging cause of nosocomial respiratory and urinary tract infections. As this is a nosocomial pathogen, every individual admitted to hospitals or undergoing antibiotic treatment has the potential risk of acquiring infection[28,29].

4. Isolation and identification methods

There is a variety of methods to assess the diversity of *Acinetobacter* spp. Several methods or combinations of methods have been found useful in delineating species[5].

The phenotypic and genotypic identification methods (biochemical systems and 16S rRNA gene sequencing) utilized in the species determination of *Acinetobacter* spp.. The 16S rRNA gene sequencing is not too conserved to distinguish all *Acinetobacter* spp.[6]. A more effective identification method is required for clinical or laboratory applications. In this case, rpoB sequencing and

Table 1. Identified *Acinetobacter baumannii* virulence factors

Virulence factor (gene)	Proposed role in the pathogenesis	Reference(s)
Porin (OmpA, Omp33-36, Omp22, CarO, OprD-like)	Induction of apoptosis in host cells, adherence and invasion of epithelial cells, biofilm formation, surface motility, serum resistance	28, 29
Lipopolysaccharide (*LPSB*)	Host immune response evasion, resistance to cationic antimicrobial peptides, triggering the host inflammatory response, reduces TLR4 signaling and desiccation survival	30
Capsular polysaccharide (*ptk* and *epsA*)	Evasion of the host immune response, growth in serum	31
Phospholipase D (A1S_2989)	Bacterial survival in vivo, serum resistance, and dissemination of bacteria	32
Penicillin-binding protein 7/8 (*pbpG*)	Biosynthesis of peptidoglycan, cellular stability, and growth in serum	31, 32
Phospholipase C	Exhibiting hemolytic action against human red blood cells and assisting in the uptake of iron	32
Outer membrane vesicles	Delivery of virulence factors to the cytoplasm of host cells, transfer of genetic material between bacterial cells	33
Acinetobactin-mediated iron acquisition system	Provides iron needed to persist in the host, causes cell apoptosis	29
FhaBC	Adherence, killing of host cells	34
Pili	Adherence, biofilm formation	34
AbeD	Killing of host cells	34
OmpR/EnvZ	Killing of host cells	28, 29, 34

Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF-MS) was evaluated as two alternative methods.

The rpoB gene has a housekeeping role, and its size differs between species[37]. The variability of the rpoB gene sequence ensures that it is impossible to design universal primers to amplify this gene for all bacteria. As a result, rpoB is more suitable for typing subspecies, and is frequently used as a multiple-locus sequence typing (MLST) locus for many bacterial species[37].

5. Antimicrobial resistance of *A. baumannii*

The severity of *A. baumannii* infections is caused by the high ability of this bacterium to survive in extreme environmental conditions through the multitude of resistance mechanisms[6]. The *A. baumannii* revealed both intrinsic and acquired resistance mechanisms based on chromosomal mutations and the acquisition of ARGs (antibiotic resistance genes) through HGT (Horizontal gene transfer)[35]. The A. baumannii antibiotic resistance is driven by multiple mechanisms[37].

Acinetobacter has impressive genetic plasticity, facilitating rapid genetic mutations and rearrangements as well as the integration of foreign determinants carried by mobile genetic elements[37]. Of these, insertion sequences are considered one of the key forces shaping bacterial genomes and evolution[37]. Additionally, *A. baumannii* can form biofilms and thus prolong its survival on medical devices, such as ventilators in ICUs[38]. However, the relationship between biofilm formation and antibiotic resistance remains unclear[38].

Biofilms are sessile microbial cells embedded in a self-producing exopolysaccharides (EPS) matrix. In biofilms, bacterial cells possess increased resistance to antibiotics or biocides, the host's immune response, antimicrobial agents, and a high ability to survive in extreme environmental conditions[6]. The impaired diffusion of antimicrobial agents causes increased bacterial resistance in biofilms due to microbial aggregation, overexpression of matrix exopolymers, and alteration of phenotypic and genotypic microbial characteristics to stress response[6,38]. The phenotypic and genotypic characteristics of bacterial cells are triggered when producing quorum-sensing signals in a cell-dependent manner, signals that allow communication between cells when significant changes in environmental conditions occur[39]. Antimicrobial agents such as antibiotics or biocides can trigger the formation of biofilms if administered at concentrations lower than the minimum inhibitory concentration (MIC)[38]. Therefore, treating infections caused by biofilm-forming bacteria requires higher doses of antibiotics and antimicrobial agents[6].

Rahbar et al. found a high rate of resistance to *A. baumannii* for ceftriaxone (90.9%), piperacillin (90.9%), ceftazidime (84.1%), and ciprofloxacin (90.9%). They reported imipenem as the most effective antibiotic[40].

A systematic review concluded that the acquisition and spread of *A. baumannii* appeared to be related to a large number of variables, the most important of which were deficiencies in the implementation of infection control guidelines and the use of broad-spectrum antibiotics[41].

Certain strains of *A. baumannii* are highly resistant to most antibiotics available in clinical practice. A number of resistance mechanisms to different classes of antibiotics are known to exist in *A. baumannii*, including β-lactamases, multidrug efflux pumps, aminoglycoside-modifying enzymes, permeability defects, and the alteration of target sites[42]. Most of these resistance mechanisms can target different classes of antibiotics. However, several other mechanisms can work together to contribute to the resistance to a single class of antibiotics. Carbapenems were the preferred treatment for MDR *A. baumannii* infections, but their prior use has led to an increased incidence of carbapenem resistance during the last years[43]. Polymyxins are now widely used as antibiotics for MDR *A. baumannii* infections. They were initially avoided due to their systemic toxicities (nephrotoxicity and neurotoxicity)[44]. Extensive drug-resistant (XDR) *A. baumannii* is called an isolate resistant to three or more classes of antimicrobials (penicillins and cephalosporins—including inhibitor combinations, fluoroquinolones, and aminoglycosides, resistant to carbapenems in most cases), while pan drug-resistant (PDR) *A. baumannii* is an XDR isolate resistant to polymyxins and tigecycline. Lately, extensively drug-

Table 2. The major resistance mechanisms of *Acinetobacter baumannii*

Drug class	Resistance mechanism	Examples
β-lactams	Inactivating enzymes	β-lactamases (AmpC, TEM, VEB*, PER, CTX-M, SHV)
Lipopolysaccharide (*LPSB*)	Carbapenemases (OXA-23, -40, -51, -58-143-like, VIM, IMP, NDM-1, -2)	
Capsular polysaccharide (*ptk* and *epsA*)	Decreased outer membrane protein expression	CarO, 33–36 kDa protein, OprD-like protein
Phospholipase D (A1S_2989)	Altered penicillin-binding protein expression	PBP2
Efflux pumps	AdeABC	
Fluoroquinolones	Target modification	Mutations in *gyrA* and *parC*
Efflux pumps	AdeABC, AdeM	
Aminoglycosides	Aminoglycoside modifying enzymes	AAC*, ‡, ANT, APH*, ‡
	Efflux pumps	AdeABC, AdeM
Ribosomal methylation	ArmA	
Tetracyclines	Efflux pumps	AdeABC, TetA*, TetB
Ribosomal protection	TetM	
Glycylcyclines	Efflux pumps	AdeABC
Polymyxins (colistin)	Target modification	Mutations in the PmrA/B two-component system (LPS modification), mutations in LPS biosynthesis genes

resistant isolates have led to the discovery of novel antimicrobials and the introduction of new treatment approaches[45]. A study by Moradi et al. showed that this group of antibiotics had low-level resistance in 2001e2007 (51.1% imipenem, 64.3% meropenem), which increased in 2012e2013 (76.5% imipenem, 81.5% meropenem[21]. Table 2 shows the different antimicrobial resistance mechanisms of *A. baumannii*.

6. Treatment aspects of infections caused by *Acinetobacter baumannii*

The most important aspect of the infection with *A. baumannii* strains is their resistance to entirely known antibiotics, suggesting the need for urgent action by the global healthcare community. Due to the high antibiotic resistance rate, this pathogen can survive for a long time in the hospital environment and spread nosocomial[1, 2].

Acinetobacter baumannii may cause pneumonia, wound infections, bacteremia, urinary tract infections and meningitis[7]. Among the identified risk factors leading to colonization or infection with *A. baumannii* (sometimes difficult to distinguish), prolonged hospitalization, ICU admission, recent surgical procedures, antimicrobial agent exposure, central venous catheter use, prior hospitalization, nursing home residence and local colonization pressure on susceptible patients are well known[22, 23].

Those infections can be treated with a combination of β-lactam and aminoglycoside. The combination of a β-lactam with an aminoglycoside appears at least synergistic *in vitro* and allows a rapid bactericidal effect[49]. Fluoroquinolones also exhibited a rapid bactericidal effect against susceptible *A. baumannii* and therefore can be used in combination with a β-lactam[46]. The increasing resistance trend observed for fluoroquinolones, aminoglycosides, and broad-spectrum β-lactams has consequently led to the use of carbapenems alone or in combination with nonclassical molecules, such as polymyxin, rifampin and sulbactam[44-46]. Tigecyline is often active against multidrug-resistant *A. baumannii*; however, recent reports described the emergence of tigecycline resistance[47]. The control of MDR in *A. baumannii* can be one of the significant challenges in clinical microbiology in the near future. Those infections can be treated with a combination of β-lactam and aminoglycoside. The combination of a β-lactam together with an aminoglycoside appears at least synergistic *in vitro* and allows a rapid bactericidal effect [48].

Minocycline, has been proposed for treating drug-resistant *A. baumannii*[49]. However, approximately 20% of *A. baumannii* isolates are not susceptible to minocycline since the introduction of minocycline,[49]. Minocycline therapy combined with colistin is effective for treating minocycline-resistant *A. baumannii* infections[48], and minocycline therapy combined with rifampicin, colistin, or imipenem has a synergistic effect in most isolates without the tetB gene[49].

Lin et al. (2014) observed that only a few effective anti-*Acinetobacter* currently available drugs, such as polymyxins and tigecycline[50].

The colistin resistance of *baumannii* isolates in MDRA (10.4%) was lower than that of rifampicin (47.8%) or tigecycline (45.5%) resistance[51]. Therefore, colistin seems to be the only effective antimicrobial agent against MDR *A. baumannii* infections. Unfortunately, the emergence of colistin-resistant *A. baumannii* strains has increased worldwide[52].

Trimethoprim-sulfamethoxazole alone effectively kills all carbapenem-resistant *A. baumannii* strains, and trimethoprim-sulfamethoxazole combined with colistin also rapidly kills all strains for up to 24 h[52].

Fluoroquinolones also exhibited a rapid bactericidal effect against susceptible *A. baumannii;* therefore, it can be used in combination with a β-lactam[46, 47]. The increasing resistance trend observed for fluoroquinolones, aminoglycosides, and broad-spectrum β-lactams has consequently led to the use of carbapenems alone or in combination with nonclassical molecules, such as polymyxin, rifampin, and sulbactam[46,53]. Tigecyline is often active against MDR *A. baumannii*; however, recent reports

described the emergence of tigecycline resistance[41,42]. It is likely that the now widely distributed blaNDM carbapenemase genes, increasingly reported in *Enterobacteriaceae*, first spread among *Acinetobacter* spp. before disseminating into *Enterobacteriaceae*[38]. *Acinetobacter baumannii* exhibits different factors potentially involved in the persistence of antimicrobial resistance in healthcare institutes (either antibiotics or antiseptics) and also shows a robust metabolism that is possibly responsible for higher survival on inorganic surfaces compared with most enterobacterial species[29,47]. Nevertheless, the current main problem with regard to the *A. baumannii* resistance is that carbapenems are often associated with multidrug or even pandrug resistance.

Since antibiotic-based therapies may become more and more limited when dealing with *A. baumannii*, alternative therapies are being explored. These experimental therapies include bacteriophage-based therapy or antibacterial peptides[44,46]. The main problem with these therapies is that their efficacy has been evaluated only in vitro. The pharmacokinetic/pharmacodynamic profiles of these compounds, including half-life, diffusion in the host organism, and potential degradation by human body fluids, limit their clinical efficacy. Accordingly, bacteriophage therapy is quite hazardous, and there is not enough data regarding the *in vivo* activity of such compounds. Moreover, control of the virus after treatment seems to be impossible. In addition, the emergence of bacteriophage-resistant strains under therapy can rapidly occur (modification of their membrane target site). However, it is believed that antibiotic-use policies and control of antibiotic resistance are crucial for controlling the emergence and spread of antibiotic resistance in *A. baumannii*[48].

7. Conclusion

Acinetobacter infections are becoming an increasingly common clinical entity which may very well affect the antimicrobial resistance of this organism worldwide. The enormous adaptability of *A. baumannii*, as well as the ability to survive in extreme environmental conditions, lead to a permanent need to unravel the diversity of mechanisms involved in the acquisition and transfer of resistance determinants.

Aminoglycosides, fluoroquinolones, and carbapenems are common antibiotics for treatment of *A. baumannii* infections. Results of this study shows that *A. baumannii* resistance to these agents increased. Also, resistance to lipopeptides such as polymyxin B and colistin are lower compared with that of other antimicrobial groups. Therefore, novel prevention and treatment strategies against *A. baumannii* infections are warranted.

Declarations

Competing interests

The authors declare that they have no conflict of interest.

Authors' contribution

All authors were involved in data collection, design of the article, interpretation of results, review, and manuscript preparation.

Funding

The authors received no financial support for the publication of this article.

Ethical considerations

The authors checked for plagiarism and consented to the publishing of the article. The authors have also checked the article for data fabrication, double publication, and redundancy.

Acknowledgments

None.

References

1. Serwecińska L. Antimicrobials and antibiotic-resistant bacteria: A risk to the environment and to public health. Water. 2020; 12(12): 3313. DOI: 10.3390/w12123313
2. Manniello MD, Moretta A, Salvia R, Scieuzo C, Lucchetti D, Vogel H, et al. Insect antimicrobial peptides: Potential weapons to counteract the antibiotic resistance. Cell Mol Life Sci. 2021; 78(9): 4259-4282. DOI: 10.1007/s00018-021-03784-z
3. World Health Organization (WHO). Antimicrobial resistance and the United Nations sustainable development cooperation framework: Guidance for United Nations country teams. 2021; Available at: https://apps.who.int/iris/handle/10665/346658
4. Prestinaci F, Pezzotti P, and Pantosti A. Antimicrobial resistance: A global multifaceted phenomenon. Pathog Glob Health. 2015; 109(7): 309-318. DOI: 10.1179/2047773215y.0000000030
5. Towner KJ. Biology of acinetobacter spp.: Acinetobacter. 1st ed. CRC Press; 1996. p. 13-36. Available at: https://www.taylorfrancis.com/chapters/edit/10.1201/9781003069263-2/biology-acinetobacter-spp-towner
6. Vrancianu CO, Pelcaru CF, Alistar A, Gheorghe I, Marutescu L, Popa M, et al. Escaping from ESKAPE. Clinical significance and antibiotic resistance mechanisms in acinetobacter baumannii: A review. Biointerface Res Appl Chem. 2021; 11(1): 8190-8203. DOI: 10.33263/BRIAC111.81908203
7. Yassin MT, Mostafa AA, Al-Askar AA, and Al-Otibi FO. Synergistic antibacterial activity of green synthesized silver nanomaterials with colistin antibiotic against multidrug-resistant bacterial pathogens. Crystals. 2022; 12: 1057. DOI: 10.3390/cryst12081057
8. Gupta N, Gandham N, Jadhav S, and Mishra RN. Isolation and identification of Acinetobacter species with special reference to antibiotic resistance. J Nat Sci Biol Med. 2015; 6(1): 159-162. DOI: 10.4103/0976-9668.149116
9. Diancourt L, Passet V, Nemec A, Dijkshoorn L, and Brisse S. The population structure of Acinetobacter baumannii: Expanding multiresistant clones from an ancestral susceptible genetic pool. PloS One. 2010; 5(4): e10034. DOI: 10.1371/journal.pone.0010034
10. Santaniello A, Sansone M, Fioretti A, and Menna LF. Systematic review and meta-analysis of the occurrence of ESKAPE bacteria group in dogs, and the related zoonotic risk in animal-assisted therapy, and in animal-assisted activity in the health context. Int J Environ Res Public Health. 2020; 17(9): 3278. DOI: 10.3390/ijerph17093278
11. Gentile V. New insights into the virulence potential of Acinetobacter baumannii. PHD Thesis. Roma Tre University. Italy. 2016; Available at: https://arcadia.sba.uniroma3.it/bitstream/2307/5981/1/PhD%20thesis_Valentina%20Gentile.pdf

12. Xiao T, Guo Q, Zhou Y, Shen P, Wang Y, Fang Q, et al. Comparative respiratory tract microbiome between carbapenem-resistant Acinetobacter baumannii colonization and ventilator associated pneumonia. Frontiers in Microbiology. 2022; 13: 782210. DOI: 10.3389/fmicb.2022.782210
13. Mendes RE, Castanheira M, Toleman MA, Sader HS, Jones RN, Walsh TR. Characterization of an integron carrying BlaIMP-1 and a new aminoglycoside resistance gene, Aac (6')-31, and its dissemination among genetically unrelated clinical isolates in a Brazilian hospital. Antimicrob. Antimicrob Agents Chemother. 2007; 51(7): 2611-2614. Doi: 10.1128/AAC.00838-06
14. Kyriakidis I, Vasileiou E, Pana ZD, and Tragiannidis A. Acinetobacter baumannii antibiotic resistance mechanisms. Pathogens. 2021; 10(3): 373. DOI: 10.3390/pathogens10030373
15. Kyriakidis I, Vasileiou E, Pana ZD, and Tragiannidis A. Acinetobacter baumannii antibiotic resistance mechanisms. Pathogens. 2021; 10(3): 373. DOI: 10.3390/pathogens10030373
16. Peleg AY, Seifert H, and Paterson DL. Acinetobacter baumannii: emergence of a successful pathogen. Clin Microbiol Rev. 2008; 21: 538-582. DOI: 10.1128/cmr.00058-07
17. Centers for Disease Prevention (CDC). Acinetobacter baumannii infections among patients at military medical facilities treating injured U.S. service members, 2002-2004. MMWR Morb Mortal Wkly Rep. 2004; 53(45): 1063-1066. Availablea at: https://pubmed.ncbi.nlm.nih.gov/15549020/
18. Brigo IR, Yamamoto LD, and Molina RJ. Community-acquired Acinetobacter baumannii pneumonia: A rare case in Brazil. Rev Soc Bras Med Trop. 2022; 55: e03012022. DOI: 10.1590/0037-8682-0301-2022
19. Sacco F, Bitossi C, Casciaro B, Loffredo MR, Fabiano G, Torrini L, et al. The antimicrobial peptide Esc (1-21) synergizes with colistin in inhibiting the growth and in killing multidrug resistant Acinetobacter baumannii strains. Antibiotics (Basel). 2022; 11(2): 234. DOI: 10.3390/antibiotics11020234
20. Falagas ME, and Kopterides P. Risk factors for the isolation of multi-drug-resistant Acinetobacter baumannii and Pseudomonas aeruginosa: A systematic review of the literature. J Hosp Infect. 2006; 64(1): 7-15. DOI: 10.1016/j.jhin.2006.04.015
21. Moradi J, Hashemi FB, and Bahador A. Antibiotic resistance of Acinetobacter baumannii in Iran: A systemic review of the published literature. Osong Public Health Res Perspect. 2015; 6(2): 79-86. DOI: Doi: 10.1016/j.phrp.2014.12.006
22. Kucukler E. Risk factors of Acinetobacter baumannii infections. Int J Infect Dis. 2014; 21: 420. DOI: 10.1016/j.ijid.2014.03.1287
23. Huang H, Chen B, Liu G, Jing R, Xianyu L, Xinhua H, et al. A multicenter study on the risk factors of infection caused by multi-drug resistant Acinetobacter baumannii. BMC Infect Dis. 2018; 18: 11. DOI: 10.1186/s12879-017-2932-5
24. Chiang DH, Wang CC, and Kuo HY. Risk factors for mortality in patients with *Acinetobacter baumannii* bloodstream infection with genotypic species identification. J Microbiol Immunol Infect. 2008; 41(5): 397-402. Available at: https://pubmed.ncbi.nlm.nih.gov/19122921/
25. Munoz-Price LS, Zembower T, and Penugonda S. Clinical outcomes of carbapenem-resistant Acinetobacter baumannii bloodstream infections: Study of a 2-state monoclonal outbreak. Infect Control Hosp Epidemiol. 2010; 31(10): 1057-1062. DOI: 10.1086/656247
26. Brahmi N, Beji O, and Abidi N. Epidemiology and risk factors for colonization and infection by Acinetobacter baumannii in an ICU in Tunisia, where this pathogen is endemic. J Infect Chemother. 2007; 13(6): 400-404. DOI: 10.1007/s10156-007-0557-0
27. Cook-Libin S, Sykes EM, Kornelsen V, and Kumar A. Iron acquisition mechanisms and their role in the virulence of Acinetobacter baumannii. Infect Immun. 2022; 90(10): e0022322. DOI: 10.1128/iai.00223-22
28. Birkle K. The role of the periplasmic chaperones SurA, Skp and DegP in fitness, outer membrane integrity, antibiotic susceptibility and virulence of Acinetobacter baumannii: Same-same, but different?. PhD Tesis. Eberhard Karls Universität Tübingen, 2021.
29. Gedefie A, Demsis W, Ashagrie M, Kassa Y, Tesfaye M, Tilahun M, et al. Acinetobacter baumannii biofilm formation and its role in disease pathogenesis: A review. Infect Drug Resist. 2021; 14: 3711-3719. DOI: 10.2147/idr.s332051
30. Moubareck AC, and Halat HD. Insights into Acinetobacter baumannii: A review of microbiological, virulence, and resistance traits in a threatening nosocomial pathogen. Antibiotics. 2020; 9(3): 119. DOI: 10.3390/antibiotics9030119
31. Fiji E, Anandharaj B, and Jijo GV. Molecular determination of virulence factor genes of Acinetobacter baumannii isolates from clinical specimens. Int J Life Sci Pharma Res. 2022; 12(3): L150-158. Available at: https://scholar.archive.org/work/pxaow2q5cvafpmvq7ux6nxvnpe/access/wayback/http://cyberdairy.info/ijlpr/index.php/journal/article/download/1221/1018
32. Tian S, Ali M, Xie L, and Li L. Genome-sequence analysis of Acinetobacter johnsonii MB44 reveals potential nematode-virulent factors. Springerplus. 2016; 5: 986. Available at: https://springerplus.springeropen.com/articles/10.1186/s40064-016-2668-5
33. Jha C, Ghosh S, Gautam V, Malhotra P, and Ray P. *In vitro* study of virulence potential of Acinetobacter baumannii outer membrane vesicles. Microb Pathog. 2017; 111: 218-224. DOI: 10.1016/j.micpath.2017.08.048
34. Astaneh SD, Rasooli I, and Gargari SL. Filamentous hemagglutinin adhesin FhaB limits A. baumannii biofilm formation. Front Biosci (Elite Ed). 2017; 9(2): 266-275. DOI: 10.2741/e801
35. Lerminiaux NA, and Cameron AD. Horizontal transfer of antibiotic resistance genes in clinical environments. Can J Microbiol. 2019; 65(1): 34-44. DOI: 10.1139/cjm-2018-0275
36. Kyriakidis I, Vasileiou E, Pana ZD, and Tragiannidis A. Acinetobacter baumannii antibiotic resistance mechanisms. Pathogens. 2021; 10(3): 373. DOI: 10.3390/pathogens10030373
37. Clark AE, Kaleta EJ, Arora A, and Wolk DM. Matrix-assisted laser desorption ionization–time of flight mass spectrometry: A fundamental shift in the routine practice of clinical microbiology. Clin Microbiol Rev. 2013; 26(3): 547-603. DOI: 10.1128%2FCMR.00072-12
38. Eze EC, Chenia HY, and El Zowalaty ME. Acinetobacter baumannii biofilms: Effects of physicochemical factors, virulence, antibiotic resistance determinants, gene regulation, and future antimicrobial treatments. Infect Drug Resist. 2018; 11: 2277-2299. DOI: 10.2147/idr.s169894
39. Ahator SD, and Zhang L. Small is mighty—Chemical communication systems in Pseudomonas aeruginosa. Annu Rev Microbiol. 2019; 73: 559-578. DOI: 10.1146/annurev-micro-020518-120044
40. Rahbar M, Mehrgan H, and Aliakbari NH. Prevalence of antibioticresistant Acinetobacter baumannii in a 1000-bed tertiary care hospital in Tehran, Iran. Indian J Pathol Microbiol. 2010; 53(2): 290-293. DOI: 10.4103/0377-4929.64333
41. Falagas ME, and Kopterides P. Risk factors for the isolation of multi-drug-resistant Acinetobacter baumannii and Pseudomonas aeruginosa: A systematic review of the literature. J Hosp Infect. 2006; 64(1): 7-15. DOI: 10.1016/j.jhin.2006.04.015
42. Morris S, and Cerceo E. Trends, epidemiology, and management of multi-drug resistant gram-negative bacterial infections in the hospitalized setting. Antibiotics. 2020; 9(4): 196. DOI: 10.3390/antibiotics9040196
43. Ahmed MM. Polymyxins: Last resort for MDR and/or XDR gram-negative infections. J Sci Res Med Biolo Sci. 2021; 2(3): 123-141. DOI: 10.47631/jsrmbs.v2i3.242
44. He J, Hong M, Xie W, Chen Z, Chen D, and Xie S. Progress and prospects of nanomaterials against resistant bacteria. J Control Release. 2022; 351: 301-323. DOI: 10.1016/j.jconrel.2022.09.030
45. Theuretzbacher U, Bush K, Harbarth S, Paul M, Rex JH, Tacconelli E, et al. Critical analysis of antibacterial agents in clinical development. Nat Rev Microbiol. 2020; 18(5): 286-298. DOI: 10.1038/s41579-020-0340-0
46. Ali T, Ali I, Khan NA, Han B, and Gao J. The growing genetic and functional diversity of extended spectrum beta-lactamases. Biomed Res Int. 2018; 2018: 9519718. DOI: 10.1155/2018/9519718
47. Nasiri MJ, Zamani S, Fardsanei F, Arshadi M, Bigverdi R, Hajikhani B, et al. Prevalence and mechanisms of carbapenem resistance in Acinetobacter baumannii: A comprehensive systematic review of cross-sectional studies from Iran. Microb Drug Resist. 2020; 26(3): 270-283. DOI: 10.1089/mdr.2018.0435
48. Ritchie DJ, and Garavaglia-Wilson A. A review of intravenous minocycline for treatment of multidrug-resistant Acinetobacter infections. Clin Infect Dis. 2014; 59(Suppl. 6): S374-S380. DOI: 10.1093/cid/ciu613
49. Yang YS, Lee Y, Tseng KC, Huang WC, Chuang MF, Kuo SC, et al. In vivo and in vitro efficacy of minocycline-based combination therapy for

minocycline-resistant Acinetobacter baumannii. Antimicrob Agents Chemother. 2016; 60(7): 4047-4054. DOI: 10.1128/aac.02994-15
50. Rodriguez CH, Nastro M, Vay C, and Famiglietti A. *In vitro* activity of minocycline alone or in combination in multidrugresistant Acinetobacter baumannii isolates. J Med Microbiol. 2015; 64: 1196-1200. DOI: 10.1099/jmm.0.000147
51. Lin MF, Lin YY, Yeh HW, and Lan CY. Role of the BaeSR two-component System in the regulation of Acinetobacter baumannii AdeAB genes and its correlation with tigecycline susceptibility. BMC Microbiol. 2014; 14: 119. DOI: 10.1186/1471-2180-14-119
52. Chang KC, Lin MF, Lin NT, Wu WJ, Kuo HY, Lin TY, et al. Clonal spread of multidrug-resistant Acinetobacter baumannii in eastern Taiwan. J Microbiol Immunol Infect. 2012; 45(1): 37-42. DOI: 10.1016/j.jmii.2011.09.019
53. Nepka M, Perivolioti E, Kraniotaki E, Politi L, Tsakris A, and Pournaras S. *In vitro* bactericidal activity of trimethoprim-sulfamethoxazole alone and in combination with colistin, against carbapenem-resistant Acinetobacter baumannii clinical isolates. Antimicrob Agents Chemother. 2016; 60(11): 6903-6906. DOI: 10.1128/AAC.01082-16